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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,348	LUKE, RICHARD WILLIAM ARTHUR	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070308*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2 and 6-12 are pending in this application.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-2 and 6-12 drawn to compounds of formula (I) wherein Y is N, corresponding composition and method of use) in the reply filed on April 17, 2008 is acknowledged. The traversal is on the ground(s) that the restriction is improper because the claimed invention meets the unity of invention requirement. This is not found persuasive because this application is a national stage application under 35 U.S.C. 371 and lacks unity of invention under PCT Rule 13.2 which states that the applicants are entitled to a compound, a process of preparation of the compound, a composition, and a method of use. The compounds of formula (I) represent patentably independent and distinct inventions as previously pointed out in office action dated July 8, 2004. In case of a single claim defining alternatives ("Markush Practice"), 'the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature'. See MPEP, Appendix AI, Annex B. In the instant case, the alternatives namely pyrimidines and pyridines are not art recognized equivalents and different issues of patentability may arise.

In order to meet unity of invention criteria for alternatives of a Markush group, the following criteria should be fulfilled:

(A) all alternatives have a common property, or activity, **and**

(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

In the instant case the compounds of formula (I) do not share a significant structural element. The claimed compounds have a pyrimidine or pyridine group attached to another heteroaryl ring having multiple variables via ethenyl or ethynyl group, which in itself is not sufficient to distinguish over prior art, see e.g., WO 01/17968. Each of structural element that is part of formula (I) contains numerous alternatives that are structurally dissimilar and therefore, the instant claims lack unity of invention. The instantly claimed invention does not meet the above unity of invention criteria because the alternatives are not art recognized equivalents and different issues of patentability may arise. Further, 37 CFR 1.475(e) states that "The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim". Furthermore, applicant did not submit evidence or identify such evidence now of record showing that the compounds of Groups I and II are obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-2 and 6-12 (all in part, i.e., formula (I) wherein Y is CR^6) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention,

there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 17, 2008.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of inhibiting Tie2 receptor tyrosine kinase activity in a warm-blooded animal or a method of producing an anti-angiogenic effect in a warm-blooded animal.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

Claims 11 and 12 read on treating a disease or condition, which has not been specified. The how to use portion of the statute has not been addressed. This means that Applicants must teach the skilled practitioner, in this case a physician, how to treat a given subject. The physician

clearly must know what diseases and what symptoms are to be treated. The specification indicates that the claimed methods of use are directed to, among other diseases, treating cancer generally.

Is extensive experimentation required on the part of a potential infringer to determine if his use of Applicants' agonists falls within the limitations of applicants' claim? *In re Kirk and Petrow*, 153 USPQ 48 (CCPA 1967). As the Supreme Court said in *Brenner v. Manson*, 148 USPQ at 696: "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." As U.S. Court of Customs and Patent Appeals stated *In re Diedrich* 138 USPQ at 130, quoting with approval from the decision of the board: "We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates."

Applicants have not demonstrated nor have they alleged there is any correlation between the *in vitro* assays they disclose in pages 26-31 and clinical efficacy against any disease. Case law is clear on this point. In an unpredictable art, such as cancer therapy, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The how to use requirement of the enablement statute, when applied to method claims 11-12, refers to operability and how to make the claimed method work "The factors to be considered (in making an enablement rejection) have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The issue is the correlation between clinical efficacy for producing an anti-angiogenic effect and Applicants' in vitro assay.

a) Determining if any particular claimed compound would produce an anti-angiogenic effect generally would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials with a number of fundamentally different diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation.

b) The direction concerning treating these diseases found in the specification merely states Applicants' intention to do so. Since no compound has ever been found that can produce an anti-angiogenic effect generally, how is the skilled physician to know what dose to use for each of the different diseases?

c) There is no working example of treatment of any rejected disease in man or animals.

d) The nature of the invention is clinical treatment of cancers generally, which involves physiological activity. The specification does not provide enablement for the treatment of cancer generally. No compound has ever been found that can treat cancers generally even though massive efforts have been directed towards this end. Since this assertion is contrary to what is known in oncology, proof must be provided that this revolutionary assertion has merits. Nearly all anticancer drugs are effective against only a limited group of related cancers. Therefore, a compound effective against cancer generally would be a revolutionary exception. Applicant is asserting that he succeeded where others have failed. Where extensive efforts have all failed, it is reasonable for the Patent and Trademark Office to require proof that the claimed invention actually works for this specific utility. It is well established that a utility rejection is proper when scope of enablement is not reasonably correlated to the scope of the claims. (*In re Vaeck*, 20 USPQ2d 1439, 1444, In re Ferens 163 USPQ 609).

In re Buting, 163 USPQ 689 establishes that even clinical tests showing that a compound found to be useful in the treatment of two types of cancers was not sufficient for a much broader range.

e) The state of the clinical arts in the cancer treatment related area is extensive with no single report of success of the ability of a single compound to treat cancers generally. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. It is beyond the skill of oncologists today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine

kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that "pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles" see page 585, col. 2, lines 33-36.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience.

g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ l8, 24 (CCPA 1970).

h) The scope of the claims involves all of the hundreds of cancers embraced by the claims. Thus, the scope of the claim is very broad. The scope of uses embraced by these claims is not remotely enabled based solely on instant compounds ability to inhibit tyrosine kinase.

MPEP 2164.0l(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

The how to use portion of the statute has not been addressed. This means that Applicants must teach the skilled practitioner, in this case a physician, how to treat a given subject. The physician clearly must know what diseases and what symptoms are to be treated. In this case, Applicants have not provided what is being treated by claims 11 and 12, who the subject is, how one can identify said subject (i.e. how one can identify a subject in need), given no specific dose,

given no specific dosing regimen, given no specific route of administration, and do not specify what diseases or symptom they intend to treat.

These claims would read on inhibiting Tie2 receptor tyrosine kinase activity in warm-blooded animals with below Tie2 receptor tyrosine kinase activity, Tie2 receptor tyrosine kinase activity inhibition in animals with normal Tie2 receptor tyrosine kinase activity, or in asymptomatic mammals with up-regulated Tie2 receptor tyrosine kinase activity. The specification fails to teach any benefit to be gained from such actions. Is extensive experimentation required on the part of a potential infringer to determine if his use of Applicants' inhibitor falls within the limitations of applicants' claim? *In re Kirk and Petrow*, 153 USPQ 48 (CCPA 1967).

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. *Genentech Inc. v. Novo Nordisk*, 42 USPQ2d 1001.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, following the definition of Q^1, it is recited:

"and wherein Q^1 is optionally substituted by … **selected from** halogeno, …., from a group of formula: $-X^1-R^7$ wherein …, **and** from a group of the formula: $-X^2-Q^2$ wherein ……., **or** from a group of the formula: $-X^3-R^{10}$ wherein ….".

The above recitation is confusing because it does not represent a proper Markush group such that the groups are recited alternatively. Similar discrepancy is observed in the definitions of R^4 and R^6, wherein it is recited "… selected from hydrogen, …., **or** from a group of the formula Q^4-X^5- …., **or** from a group of the formula Q^5-X^6- …., **or** from a group of formula $-X^7-Q^6$ …, from a group of the formula $-X^8-R^{16}$ ... , **and** from a group of the formula $-X^9-Q^7$".

See MPEP § 2173.05(h): "When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material **selected from** the group consisting of **A, B, C and D**" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper".

The recitation in the claim is confusing because it contains both the terms "**and**" as well as "**or**" separating the groups recited in the substituent list for Q^1. Appropriate correction consistent with the MPEP instructions of a proper Markush group are required.

Allowable Subject Matter

Claims 1-2 and 6-10 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action. The references of record do not teach or fairly suggest the instantly claimed compounds.

Receipt is acknowledged of the Information Disclosure Statement filed on March 8, 2007 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

July 8, 2008